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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant : Arne Elof Brändström

Serial No. : 854,739 Examiner : J. Fan

Filed : April 21, 1986 Group Art Unit : 121

For : NOVEL COMPOUNDS

DECLARATION UNDER RULE 132

Hon. Commissioner of Patents and Trademarks

Washington, D.C. 20231

S I R :

I, Åke Gunnar Pilbrant, declare that:

1. I am a citizen of Sweden, residing at Snödroppevägen 6, S-434 00 Kungsbacka, Sweden.

2. I was awarded the degree of Master of Science in Pharmacy in 1965, and the degree of Farmacie Licenciat in 1969.

3. I was employed by AB Kabi, Stockholm, Sweden from 1969-1979 as Head of the Section for Development of Nonparenteral Dosage forms, Department of Pharmaceutics. I have been employed by AB Hässle, Mölndal, Sweden from 1979 to the present as Head of the Section for Product Development, Gastrointestinal Products. I am the author or co-author of about fifteen papers in the field of pharmaceutical chemistry, pharmacy, biopharmacy and pharmacokinetics.

4. I am familiar with the U.S. Patent Application Serial No. 854,739 of Brändström. I am also familiar with the

U.S. Patent Application Serial No. 640,020 of Brändström, the parent application of the present application, and with the Official Action dated October 24, 1986, in said application No. 854,739, in which the claims of the application were rejected.

5. I have executed a Declaration under Rule 132 in the present application No. 854,739.

6. I have caused a number of tests to be run to compare the stability of base addition salts of omeprazole with neutral omeprazole under two different storage conditions.

7. Sodium, calcium and magnesium salts of omeprazole were prepared according to the method described in U.S. Patent Application Serial No. 854,739. Samples of these salts, and of neutral omeprazole were placed in amber glass bottles, sealed with snap-cap polyethylene closures, and stored at 50°C. A second set of samples were placed in open petri dishes and stored at 37°C and 80% relative humidity. The chosen test conditions are recommended test conditions by US Food and Drug Administration in "Draft Guideline for Stability Studies for Human Drugs and Biologics" published in 1984. A copy of said Guideline is enclosed as Exhibit A. The Guideline, p.4 under paragraph B, states that

"A program for the stability testing of the bulk drug substance should include storage in open and closed containers at ambient temperature and under stressed conditions. Stress testing conditions ordinarily include variable temperature (e.g., 5°, 50°, 75°C), humidity where applicable, (e.g., 75 percent or greater),...".

The said FDA Guideline refers on page 4 under paragraph B to a monograph by Connors K.A., Amidon G.L. and Kennon L. "Chemical Stability of Pharmaceuticals", John Wiley & Sons, New York 1979. A copy of pages 108 and 109 of the said monograph is enclosed as Exhibit B. On the said pages 108-109 a "stability protocol" is discussed and the above conditions for stability testing exemplified, together with typical sampling times.

The test conditions used in the present Declaration accordingly conform with the relevant FDA Guideline and will give information regarding the stability of tested compounds under stressed temperature conditions as well as under stressed humidity conditions.

8. Samples were withdrawn from each test container at time zero, and after 1, 3 and 6 months of storage. Magnesium and calcium salts were analyzed after 1.5 months rather than 1 month of storage.

9. The withdrawn samples were made into solutions containing 0.12 mg/ml of omeprazole by extraction with 25.0 ml of ammonia-methanol solution (6.0 ml conc. ammonia diluted to 100 ml with methanol) diluted to 1 liter with methylene chloride. The solutions were analyzed by HPLC using the extraction solvent as the mobile phase to determine the amount of degradation products.

10. Degradation of omeprazole was determined from the amount of degradation products (by-products) formed and shown in Table 1 for each of the compounds tested.

Table 1 gives the total amount of by-products found

after storage of omeprazole in neutral form for a given period of time, compared with the total amount of by-products formed after storing of the sodium, magnesium and calcium salt of omeprazole.

It is the stability data obtained after long term storage, that is after at least six months, that constitute the essential result of the tests.

Table 1

Total amount of by-products found after storage of omeprazole and omeprazole salts. The results are given as percent of intact omeprazole (peak area percent)

Storage time, months	Storage Conditions °C/% r.h.	Omeprazole	Omeprazole sodium salt	Omeprazole magnesium salt	Omeprazole calcium salt
0	-	0.2	0.1	0.2	0.2
1*	+50	0.2			
	+37/80	0.2	0.1	0.3	1.5
3	+50	1.0	0.1	0.4	0.9
	+37/80	0.3	0.8	0.4	1.7
6	+50	>4	0.1	0.6	1.1
	+37/80	>6	1.2	0.7	1.7

* The magnesium and calcium salts were analysed after 1.5 months storage.

It is seen in Table 1 that after six months storage, the neutral omeprazole test substance contains more than 4 (test at 50°C) and more than 6 (test at 37°C and 80% relative humidity) percent by-products. By contrast, the amount of

by-products after six months in the tested omeprazole salt preparations ranges in the test at 50°C from 0.1% (the sodium salt) to 1.1% (the calcium salt), and the amount of by-products at six months in the test at 37°C and 80% relative humidity ranges from 0.7 (the magnesium salt) to 1.7 (the calcium salt). Thus, the amount of by-products formed in neutral omeprazole after six months is at least 4 times (4:1.1) higher than in the tested salts, in the test at 50°C, as well as in the test at 37°C and 80% relative humidity (6:1.7).

11. The seemingly inconsistent test results in Table 1 after storage for 1(1.5) and 3 months may be explained by the following factors:

a) Differences in surface reactivity.

Omeprazole substance was crystallized from an organic solvent system and dried. In order to increase the surface area of the substance it was micronized (mean particle size about 3 um) in air jet milling apparatus. The milling makes the powder cohesive and also renders it a very hydrophobic surface.

Omeprazole calcium salt was prepared by reacting one equivalent of omeprazole substance with approximately one half equivalent of anhydrous calcium chloride in water. The precipitate was collected, washed, dried and milled. This procedure gives particles which have a hydrophilic surface.

When these two substances are exposed to an accelerated storage condition of 37°C, 80% relative humidity they react differently with regards to water absorption.

Omeprazole micronized substance with its hydrophobic surface reacts slowly and it takes quite some time before

water has been adsorbed to the total surface, where it can fully exert its effect on the degradation of omeprazole.

Omeprazole calcium salt with its hydrophilic surface adsorbs water rapidly which starts a degradation reaction at once. This applies also to the tested sodium and magnesium salts.

b) The tested substances are not totally pure initially, which might influence the stability. The substances were tested by liquid chromatography and UV-detection. The sum of impurities and degradation products was calculated assuming the same molar absorbtivity as omeprazole. The small differences in the sum of by-products, obtained at low levels, must therefore be regarded as less significant compared to the differences obtained after six months.

Consequently, a comparison of the long term storage stability of these substances should be based on results obtained after at least 6 months of storage. A real difference in stability between omeprazole and the salts is seen after six months of storage as shown in Table 1. The enclosed chromatograms (Figures 1 and 2) show omeprazole after 1 and 6 months at 37°C and 80% relative humidity and omeprazole calcium salt initially and after 6 months at the same conditions. All chromatograms are evaluated using the same scale expansion. It is obvious that the chromatogram of omeprazole contains significantly more and larger by-peaks compared with the chromatogram of the calcium salt after 6 months of storage.

12. In the stability evaluation of bulk drug substances a number of parameters are studied. Critical parameters in all stability studies are the rate of formation

of degradation products and colour changes. In the judgement of the stability of finished drug products most medical authorities (e.g. FDA) will accept degradation products up to an amount of about 0.5% of the amount of active drug. If the amount of degradation product is greater than 0.5%, the degradation product has to be identified, synthesized and may have to be passed through a full safety evaluation including long-term toxicological studies in at least two animal species. From this follows that even a small difference in the stability profile of tested compounds can mean all or nothing with regard to their usefulness as drugs.

Moreover, drug substances, which degrade to heavily coloured degradation products, can be limited for use in finished drug products by the colour change itself even if the amount of degradates is less than 0.5% of the active drug. An objective measure of the discolouration is the spectrophotometric absorbance of a solution at the wavelength of visual light (440-500 nm). The most frequently used wavelength is 440 nm. In order to study possible colour changes, samples of batches of substances given in Table 1 were stored at 25°C. Samples were withdrawn at the times given in Table 2 and made into 2% solutions. The spectrophotometric absorbance of the solutions was measured at 440 nm or 500 nm. At one occasion the absorbance was measured at both 440 and 500 nm in order to get an estimation of the relative absorptivity at the respective wavelength. The results are given in Table 2.

Table 2. Absorbance of 2% solutions of test compounds at 440 nm and 500 nm using 1-cm cells.

	ABSORBANCE			
Storage at 25°C, months	Omeprazole		Omeprazole sodium salt	Omeprazole magnesium salt
	440 nm	500 nm	440 nm	440 nm
24	0.44*	0.22		
25			0.01	
26				0.06
36	1.68	0.84		

* Calculated from the difference in molar absorptivity between 440-500 nm after 36 months storage.

As can be seen from Table 2 there is a marked difference in the discolouration of the neutral omeprazole as compared to the base addition salts after about 2 years storage (24, 25 and 26 months). The absorbance value of 0.44 for the 2 % solution of omeprazole in neutral form means a distinctly coloured (red) solution, while the absorbance values of 0.01 and 0.06 for the 2 % solutions of the sodium and magnesium salts, respectively, indicate visually practically colourless solutions.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent thereon.

Dated: April 23, 1987

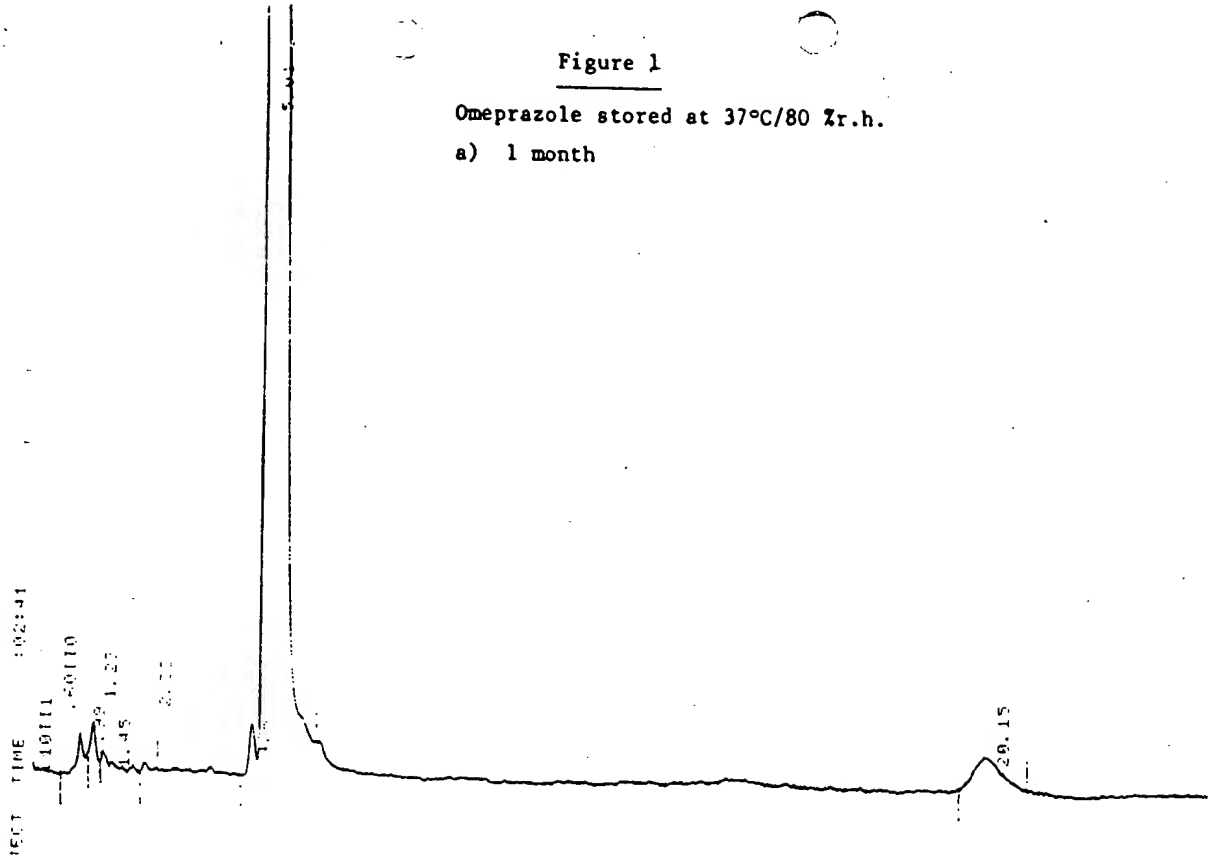
Åke Gunnar Pilbrant

ÅKE GUNNAR PILBRANT

Figure 1

Omeprazole stored at 37°C/80 %r.h.

a) 1 month



b) 6 months

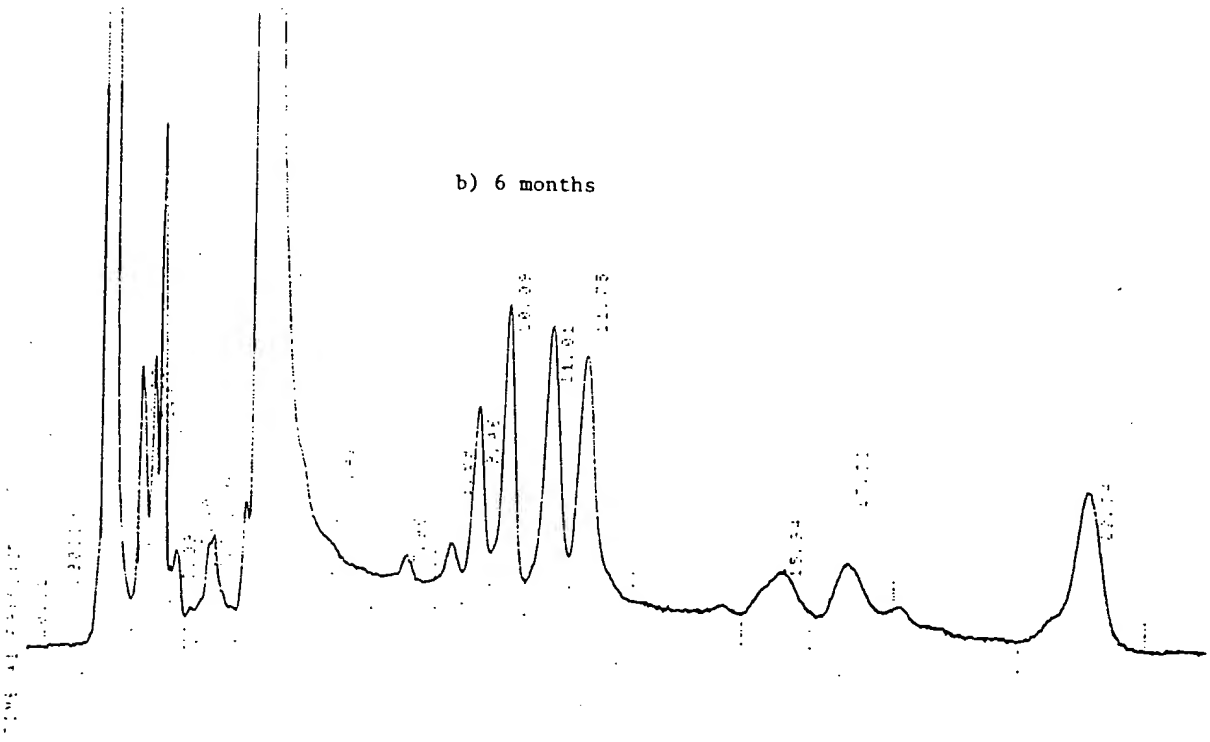
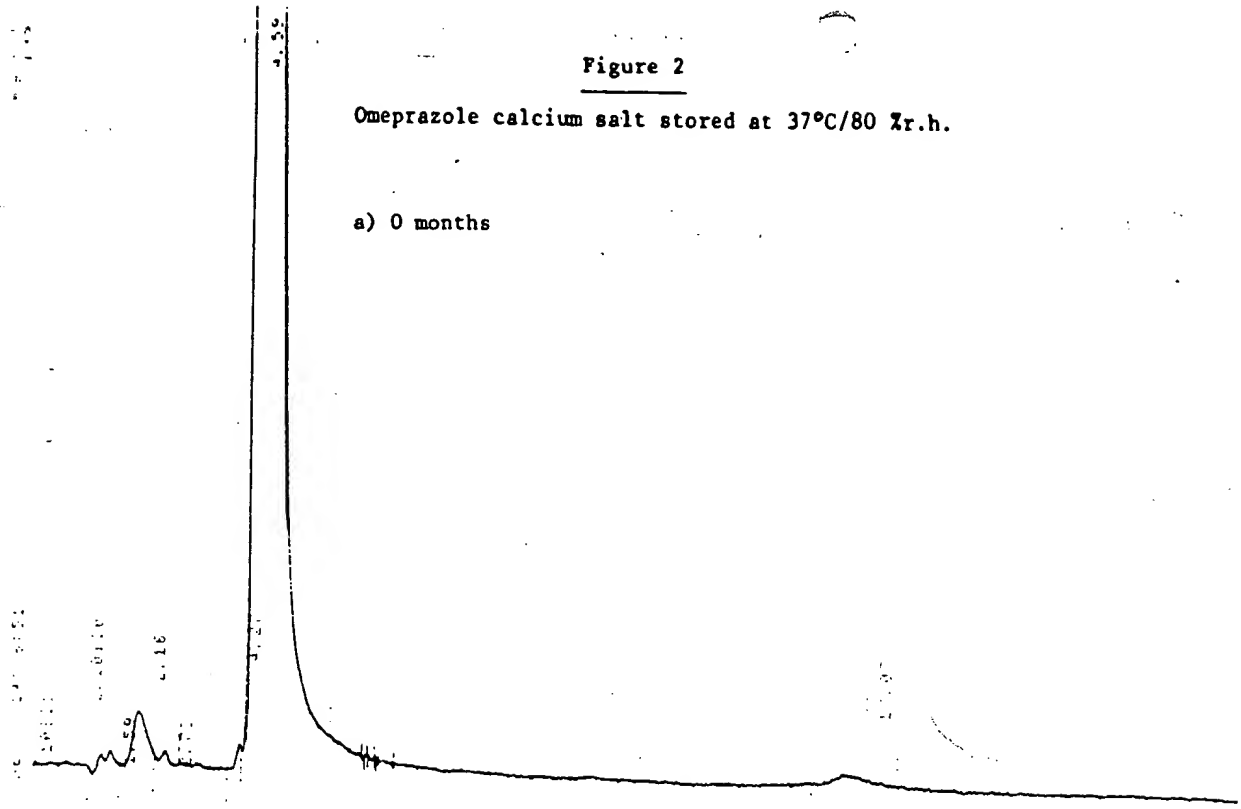


Figure 2

Omeprazole calcium salt stored at 37°C/80 %r.h.

a) 0 months



b) 6 months

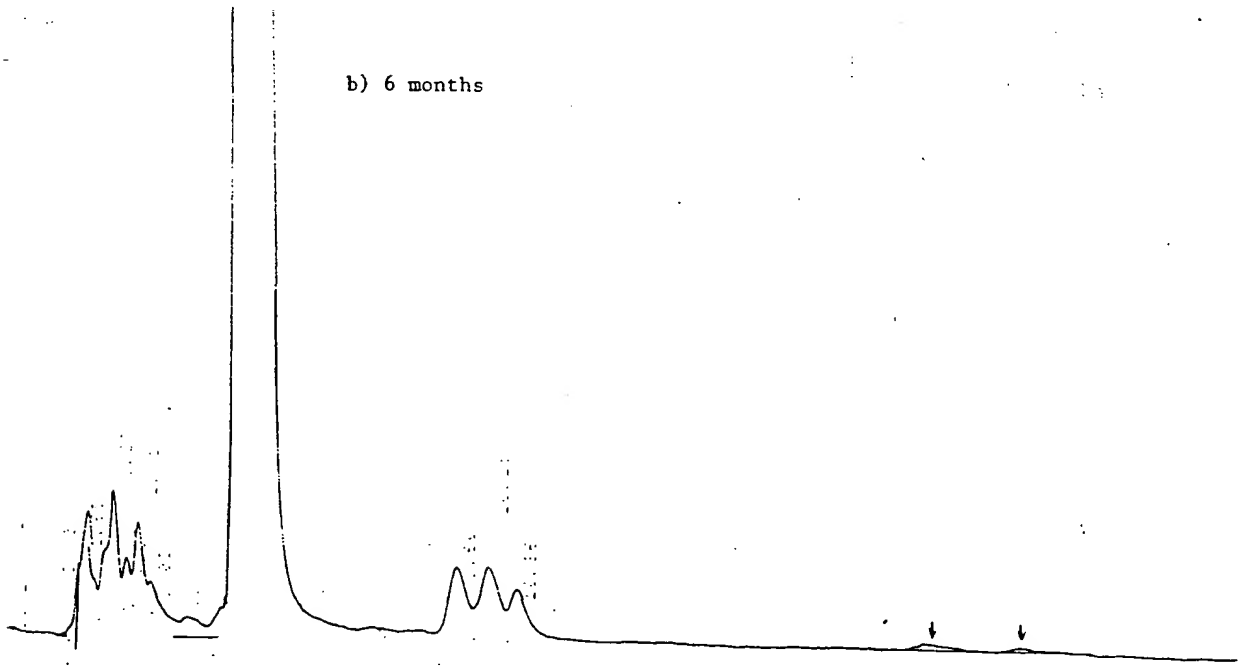


Exhibit A

DRAFT GUIDELINE FOR STABILITY STUDIES FOR HUMAN DRUGS AND BIOLOGICS

March 1984

Center for Drugs and Biologics
Office of Drug Research and Review and
Office of Biologic Research and Review
Office of Drug Standards
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Table of Contents

I. DEFINITIONS

Accelerated Testing: Studies designed to increase the rate of chemical or physical degradation of a drug substance or drug product by using exaggerated storage conditions. The purpose is to determine kinetic parameters, if possible, and/or to predict the tentative expiration dating period. This term is often used synonymously with "stress testing."

Commitment: A signed statement by an applicant of an New Drug Application (NDA), Paper NDA, Abbreviated New Drug Application (ANDA), Form 5 or 6, or Biological Product License Application (PLA) to conduct (or complete) prescribed studies after approval of an application. A commitment to obtain data may be accepted in lieu of the data themselves, when available data do not cover the full expiration dating period for the specific product/container-closure system, but there are sufficient supporting data to predict a favorable outcome with a high degree of confidence, e.g., when a new drug application is approved with stability data available only from experimental or pilot lots (not production lots) or when a supplement is approved with data that do not cover the full expiration dating period. A commitment constitutes an agreement to:

- conduct or complete the desired studies,
- submit results as they become available, or as specified by Food and Drug Administration (FDA), and
- promptly withdraw from the market any lots that do not meet approved specifications, and must be reported to FDA under 21 CFR 310.300(b)(1).

Drug Product: As defined under 21 CFR 210.3(b)(4), "drug product" means a finished dosage form, e.g., tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients.

Expiration Date: The date placed on the immediate container label of a drug product that designates the date through which the product is expected to remain within specifications. If the expiration date includes only a month and year, it is expected that the product will meet specifications through the last day of the month.

Expiration Dating Period: The interval of time that a drug product is expected to remain within specifications as determined from stability studies on a limited number of batches of the product. The expiration dating period is used to establish the expiration date of individual batches.

Paper NDA: An unofficial term referring to an NDA duplicating a previously marketed post-1962 product where the evidence of safety and effectiveness has been taken primarily from the published

literature. From a chemistry viewpoint, the term has no implication, as the requirements are identical to any other NDA.

Primary Stability Data: Data on the drug product stored in the proposed container-closure system for marketing at temperatures specified on the label.

Random Sample: A selection of units chosen from a larger population of such units in such a way that the probability of inclusion of any given unit in the sample is defined. In a simple random sample each unit has equal chance of being included. This differs from a haphazard sample in that for haphazard samples the probability of inclusion cannot be calculated. Random samples are usually chosen with the aid of tables of random numbers found in many statistical texts.

Stability-Indicating Methodology: Analytical methods that will quantitatively measure the characteristic structural and chemical properties of each active ingredient of a dosage form and distinguish them from their degradation products so that the active-ingredient content can be measured.

Stability: The capacity of a drug to remain within specifications established to assure its identity, strength, quality, and purity.

Strength: A quantitative measure of active ingredient, as well as other ingredients requiring quantitation, such as alcohol and preservatives. Also, see 21 CFR 210.3(a)(16).

Stress Testing: See "Accelerated Testing," page 1.

Supportive Stability Data: Data, other than primary stability data, such as stability data on investigational formulations not proposed for marketing, accelerated studies on the bulk drug substance, literature data, references to other submissions on file with the agency with appropriate letters of authorization, accelerated studies on the proposed drug product for marketing, information regarding test results on containers, and other scientific rationale to support the recommended storage conditions in the labeling.

Tentative Expiration Dating Period: A provisional expiration dating period determined by projecting results from less than full term data (such as accelerated studies) using the drug product to be marketed in the proposed container-closure system.

II. INTRODUCTION

Throughout this guideline reference is made to various IND and NDA requirements and to documents such as amendments and supplements submitted to new drug applications. FDA regulations relating to IND's and NDA's are in process of revision. Any revisions of these regulations will be reflected in subsequent versions of the

guideline.

This guideline provides:

- recommendations for the design of stability studies to establish appropriate expiration dating period(s) and product storage requirements (Section III), and

- recommendations for submission of stability information and data to the Center for Drugs and Biologics (CDB) for investigational new drugs and biologics (Section IV), new drug applications (Section V), and product license applications (Section VI).

This guideline should not be interpreted as imposing mandatory requirements [21 CFR 10.90(b)]. It does, however, describe the data and information considered desirable and acceptable by the agency in demonstrating the stability of drug products. It is intended to provide a means of meeting the regulatory requirements as listed below:

- IND's	21 CFR 312.1[312.23(a)(7)]
- NDA's	21 CFR 314.1(c)[314.50]
- ANDA's	21 CFR 314.1(f)[314.55]
- Form 6	21 CFR 431.1[341.55]
- Form 5	21 CFR 431.17[314.50]
- PLA's	21 CFR 601.2 --
- Supplements	21 CFR 314.8[314.70]

NOTE: The numbers in brackets refer to the proposed revision of the NDA and IND regulations (47 FR 46622, October 19, 1982 and 48 FR 26720, June 9, 1983).

This guideline provides a means of developing expiration dating from at least three lots (from different batches) in order to assure a statistically acceptable level of confidence for the period proposed. It is important, however, to realize that the manufacturer has the responsibility to confirm estimated expiration dating periods by continual assessment of stability properties from future lots. Such continuing confirmation of the expiration dating period should be an important consideration in the manufacturer's stability program.

III. DESIGN AND INTERPRETATION OF STABILITY STUDIES

The proposed revision of the NDA regulations in Section 314.70(d)(47 FR 46622, October 19, 1982) would permit an extension of the expiration date based on full shelf-life data obtained from an approved protocol and filing of data in annual reports. Submission of a supplemental application for FDA approval would not be required. The proposed revision empnasizes the importance of properly designing a stability study, as only use of an approved

protocol would entitle the applicant to proceed without a supplemental application. The design of the protocol should consider the methodology for determining the stability of the bulk drug substance and drug product and the statistics relating to sampling and data analysis.

A. Methodology Considerations

It is essential that stability indicating methods be used throughout all stability studies. The methodology should be validated by the manufacturer (and the accuracy and precision established) and described in sufficient detail to permit validation by FDA laboratories [1].

B. Bulk Drug Substance Profile

Stability information on the bulk drug substance is of value in anticipating problems which may be encountered in the formulation and storage of drug products as well as in establishing storage conditions and an expiration dating period for the bulk drug substance. The stability of the bulk drug substance is also an important consideration when establishing the expiration date on a batch of drug product prepared from aged bulk drug substance.

Stability studies on the bulk drug substance are needed when adequate stability information is unavailable either from prior studies or from the literature [2]. A program for the stability testing of the bulk drug substance should include storage in open and closed containers at ambient temperature and under stressed conditions. Stress testing conditions ordinarily include variable temperature (e.g., 5°, 50°, 75° C), humidity where applicable, (e.g., 75 percent or greater), and exposure to electromagnetic radiation (e.g., 190-380nm, ultraviolet, and 380-780nm, visible) and to fluorescent light (e.g., 500-2000 footcandles) [3-6]. It is also suggested that the following conditions, frequently encountered in drug product formulations, be evaluated in studies on solutions or suspensions of bulk drug substances:

- acidic and alkaline pH,
- high oxygen and nitrogen atmospheres, and
- the presence of added substances such as chelating agents and stabilizers.

It is important to detect, isolate, and identify degradation products. Degradation products should be quantified and the reaction kinetics established, if possible.

C. Drug Products

Stability studies on samples from production-size batches of the finished dosage form in the market package stored at the temperature stated on the label are ordinarily required but are not usually adequate without other information (e.g., stress testing) for assignment of an expiration date. Stress testing of the drug product is frequently used to identify potential problems that may be encountered during storage and transportation and to provide an estimate of the expiration dating period. Other special studies may be of value for specific drugs and/or dosage forms (see III.C.7.a-m, below).

When designing stability studies, the following should be considered:

1. Container-Closure

Stability data should be developed for each type of immediate container and closure proposed for marketing the drug that differs in composition and/or design (e.g., wall thickness, torque, etc.), including child-resistant and tamper-resistant closures, regardless of similarities in cap liners. Physician's samples should also be included in the stability studies if their container-closure system is different from the market package. The possibility of interaction between drug and container-closure system and the introduction of leachables into drug formulations during storage should be assessed by sensitive quantitative procedures. This is necessary even if the containers and closures meet suitability tests to protect drug integrity such as those outlined in the United States Pharmacopeia (U.S.P.) for plastic containers and rubber or plastic closures.

For most solid dosage forms stability data need only be obtained for the smallest and the largest container-closure system to be marketed, providing that any intermediate size container-closure systems are of identical composition. Special attention should be given to all sizes of multiple-dose containers such as aerosols and parenterals (see separate entries).

Where package container sealant integrity is to be assessed, higher than 75 percent relative humidity may be appropriate to stress its adhesive properties at 37°C (e.g., blister units and strip packages).

2. Extreme Temperature Fluctuations

A study of the effects of temperature fluctuation as appropriate for the shipping and storage conditions of the products should be considered, i.e., the packaged drug

should be cycled through temperature conditions that simulate the fluctuation that may be encountered once the drug product is in distribution channels. For example, it is suggested that all liquid preparations--injections, solutions, suspensions, and semi-solid preparations (creams, ointments, and pastes)--be subjected to freezing temperatures for at least seven days, and these observations should be utilized for appropriate labeled storage conditions or warning statement(s).

3. Storage Temperatures

The actual storage temperatures (numerical) used during stability studies should be specified.

4. Effects of Opening and Closing Containers

The effect on stability brought about by opening and closing the container should be assessed and compared with the stability pattern developed from unopened-container studies. The effect of opening and closing the container is simulated by sampling from the same containers at all scheduled test periods for as long as the contents permit rather than sampling unopened containers at each test period.

5. Microbial Quality

Drug products containing preservatives to control microbial contamination should have the preservative content monitored at reasonable intervals throughout the projected expiration dating period of the product. This may be accomplished by performing microbial challenge tests (e.g., Antimicrobial Preservatives Effectiveness test of the U.S.P., which is applicable to unopened containers) and by performing chemical assays for the preservative. When the minimum quantity of preservative to achieve effective microbial control has been determined, chemical assays may be adequate providing periodic challenge tests are performed [7]. It is particularly important to consider the adequacy of the preservative system under conditions of use for multidose vials [8].

Those preparations requiring control of the microbial quality that do not contain preservatives should be tested at specific intervals throughout the projected expiration dating period according to the release specification for bioburden (e.g., Microbial Limits Tests of the U.S.P.), which includes a limit for total microbial count and for the absence of Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Salmonella species. In addition, it is recommended that topical preparations be tested for the absence of Pseudomonas cepacia, Aspergillus

niger, and Candida albicans as well as any other topical pathogens that may be identified as potentially harmful. Simulated use tests on topical preparations packaged in jars and on ophthalmics are desirable.

6. Degradation Products

When degradation products are identified, the following information should be submitted:

- chemical structure,
- cross-reference any available information about biological effect and significance at the concentrations likely to be encountered,
- procedure for isolation and purification,
- mechanism of formation, including order of reaction (See III.D.1.c., below)
- physical and chemical properties,
- specifications and directions for testing for their presence at the levels or concentrations expected to be present, and
- indication of pharmacological action or inaction.

7. Design Considerations for Specific Dosage Forms

a. Tablets: A stability study should include tests for the following characteristics of the tablet: appearance, friability, hardness, color, odor, moisture, strength, and dissolution.

b. Capsules: A stability study should include tests for the following characteristics: strength, moisture, color, appearance, shape, brittleness, and dissolution.

c. Emulsions: The following characteristics should be examined at each sampling interval: appearance (such as phase separation and color), odor, pH, viscosity, and strength. It is recommended that a heating/cooling cycle be employed, e.g., between 4° and 45° C [9 and 10].

d. Oral Solutions and Suspensions: The following characteristics should be examined at each sampling period: appearance (precipitate, cloudiness), strength,

pH, color, odor, redispersibility (suspensions), and clarity (solutions). Liquids and suspensions should be stored both upright and inverted in order to determine whether contact of the drug with the closure system affects product integrity.

After storage, samples of suspensions should be prepared for assay in accord with the recommended labeling under "Directions for Use".

e. Oral Powders: Most oral powders are marketed for reconstitution prior to administration. The following characteristics of the powder should be examined at each sampling period: appearance, strength, color, odor, and moisture. The reconstituted product should be prepared in accord with the recommended labeling under "Directions for Use". Specific characteristics to be examined on the reconstituted material should include: appearance, pH, dispersibility, and strength throughout the recommended storage period.

f. Metered Dose Inhalation Aerosols: Characteristics that should be examined in a stability study for all container-closure sizes include the following: strength (mg/ml), delivered dose (mg/valve actuation), number of (metered) doses, color, clarity (solutions), particle size (suspensions), loss of propellant, pressure, and valve corrosion [11].

Because the container contents are under pressure, filled containers must be checked for loss in weight over the expiration dating period. For suspensions, aggregate (or solvate) formation may lead to clogged valves, or the delivery of a pharmacologically inactive dose. Corrosion of the metering valve or gasket deterioration may adversely affect the delivery of the correct amount of drug substance.

As the drug product is intended for use in the lungs, it is important to consider at least the initial release specifications for the microbial limits (CFU/gram formulation) of total aerobic count, Gram-negative rods, and coagulase-positive Staphylococcus.

g. Topical and Ophthalmic Preparations: Included in this broad category are ointments, creams, lotions, pastes, gels, solutions, and non-metered aerosols for application to the skin. For stability studies of topical ointments, creams, lotions, solutions, and gels the following characteristics should be examined for all sizes as appropriate to the dosage form: appearance (clarity, color, homogeneity), odor, pH,

resuspendibility (lotions), consistency, particle size, strength, and weight loss (plastic containers).

Ointments and creams in containers larger than 3.5 grams should be assayed by sampling at the surface, middle, and bottom of the container. In addition, tubes should be sampled at other sites, e.g., near the crimp.

Evaluation of non-metered aerosols should include the following: appearance, odor, strength, pressure, weight loss, net weight dispensed, delivery rate, and spray pattern.

Evaluation of ophthalmic ointments, solutions, and suspensions should include as appropriate to the dosage form: appearance, odor, consistency, pH, resuspendibility, particle size, homogeneity (suspensions, creams, and ointments), strength, and sterility.

h. Small Volume Parenterals: Small volume parenterals include an extremely wide range of preparations and container-closure types. Each should be included in the stability study. Evaluation of these products should include at least the following: strength, appearance, color, clarity (freedom from visible foreign matter), pH, and sterility (at reasonable intervals). Stability studies on powder products should demonstrate that the residual moisture content remains within acceptable limits and that the product is stable throughout the recommended storage period. The stability of reconstitued freeze-dried products should also be determined.

Parenterals (except ampules) should be stored both upright and inverted in order to determine whether contact of the drug with the closure system affects product integrity.

i. Large Volume Parenterals: Stability tests for LVP's are similar to those appropriate for small volume parenterals. All container-closure sizes should be studied. A minimum evaluation should include the following: strength, appearance, color, clarity, particulate matter (U.S.P. or equivalent), pH, volume (plastic containers), extractables (plastic containers), and sterility (at reasonable intervals).

Continued assurance of sterility for all sterile products may be assessed by a variety of means, including examination of the container-closure system, testing for preservatives (if present), or sterility testing (at reasonable intervals).

For terminally sterilized drug products a specification for maximum process parameters should be provided. Stability studies should evaluate and support the maximum release specification for process lethality (e.g., F_o, Mrads, etc.).

These products should be stored both upright and inverted in order to determine whether contact of the drug with the closure system affects product integrity.

j. Suppositories: Suppositories should be evaluated for strength, melting range, appearance, and dissolution. The effect of aging may also be observed from a hardening of the suppository and a polymorphic transformation of the drug substance; therefore, control and stability testing should include dissolution time at 37° C.

k. Drug Additive: For any drug that is intended for use as an additive to another drug, the possibility of incompatabilities exists. In such cases, the product labeled to be administered by addition to another drug (e.g., parenterals, aerosols) should be studied for stability and compatability in admixture with the other drug.

A suggested protocol should provide for tests to be conducted at 0-, 6- to 8-, and 24-hour intervals. These should include:

- assay of the drug and additive,
- pH (especially for unbuffered LVP's) color, clarity, and
- interaction with the container.

l. Intrauterine Devices and Vaginal Devices Regulated as Drugs: Stability testing for intrauterine devices (IUD's) should include the following tests: deflection of horizontal arms or other parts of the frame if it is not a T-shaped device (frame memory), tensile strength of the withdrawal string, and integrity of the package, i.e., seal strength of the pouch and sterility of the device.

If the device contains a drug reservoir from which drug diffuses through a controlled release membrane, it should be tested for total drug content, decomposition products, and in vitro drug release rate in addition to the above tests.

Vaginal devices such as a doughnut shaped silastic or other polymeric matrix containing a drug uniformly

dispersed throughout the matrix must be checked for in vitro drug release rate and extraneous extractable substances to establish stability and drug compatibility with the matrix.

m. Biological Products: In addition to other parameters described for specific dosage forms, it is required for biological products that potency be a measure of biological activity. Generally, the official potency test (21 CFR Parts 600-680) or the potency test described in the manufacturer's approved license application for a given product will be adequate for potency determination.

N.B! Solid dosage forms, e.g., tablets, capsules, suppositories, powders (oral and parenteral), should be assayed for concentration per unit dose and per unit weight, when possible. This will permit more accurate assessment of product stability by explaining data fluctuations caused by variations in filling, tableting, etc. during manufacture.

D. Statistical Considerations

Proposed changes in the NDA regulations (47 FR 46622, October 19, 1982) permit a drug sponsor to take certain actions on the basis of an approved stability study protocol, such as extending an expiration dating period based on full shelf-life data without prior approval of a supplemental application by including the change in the next annual report under 21 CFR 314.80(c)(4)(iv). For this reason, a stability study protocol must describe not only how the stability study is to be designed and carried out, but also the statistical methods to be used in analyzing the data. An acceptable approach is described in part 2, below. If the sponsor wishes to use an alternative statistical procedure, it must be described in the stability study protocol. Part 1 of this section describes specific design features of stability studies that are pertinent to the statistical analysis.

1. Design Considerations for Long-Term Studies Under Ambient Conditions (Non-Accelerated Data)

The design of a stability study is intended to establish, on the basis of testing a limited number of batches of a drug, an expiration dating period applicable to all future batches of the drug manufactured under similar circumstances. This approach assumes that inferences drawn from this small group of tested batches extends to all future batches. Tested batches must, therefore, be representative in all respects (e.g., formulation, container/closure system, manufacturing process, age of bulk material, etc.) of the population of all production batches of that drug and conform with all quality specifications.

The stability study should be able to identify sources of variability and to quantify variability of individual dosage units, container-closure systems, and batches, as well as variability inherent in the laboratory test methodology. The degree of variability affects the confidence one might have in the ability of a future lot to remain within specifications until its expiration date.

a. Batch Sampling Considerations: Ideally, the batches selected for stability studies should constitute a random sample from the population of production batches already produced. In practice, the batches tested to establish the expiration dating period are usually the first batches produced, and there is a possibility that future changes in the production process will result in the obsolescence of the initial stability study conclusions. For this reason, additional batches should be subjected to stability studies whenever a substantial change occurs in the production process or formulation.

For unit dosage forms, such as solid oral dosage forms, variability in test values may be attributed both to assay and to unit-to-unit differences. For characterizing the batch average as a function of storage time, composites may be tested rather than individual units. However, if it is desired to characterize the unit-to-unit variance, then individual units must of course be tested. Variability of test results on bulk solutions, which are considered homogeneous, may be attributed solely to assay variance.

A sufficient sample of the batches should be taken to adequately assess within batch and between batch variability and to test the hypothesis that a single expiration dating period for all batches is justifiable. At least three batches and preferably more should be tested to allow for some estimate of batch to batch variability.

Testing of a single batch does not permit assessment of batch-to-batch variability, and testing of two batches provides an unreliable estimate. Although it is true that more data (batches) result in a more precise estimate, economic considerations prevent unlimited collection of data. Thus, the recommendation that at least three batches be tested is a compromise between statistical and economic considerations.

b. Container-Closure and Drug Product Sampling Considerations: Selection of drug products from the batches chosen for inclusion in the stability study

should be carried out in such a manner as to ensure that the samples chosen are representative of the batch as a whole; that is, they should be sampled randomly. At least two containers should be chosen from each batch at each sampling time.

In deciding how to sample the individual dosage units for assay, consideration should be given to the possible variability associated with the product. As a rule, the sampling of dosage units from a given container should be done randomly, with each dosage unit having an equal chance to be included in the sample. In the case of large containers, it may be suspected that dosage units near the cap of a bottle may have different stability properties than dosage units located in other parts of the container. In this case, it may be desirable to sample dosage units from all parts of the container suspected of giving different stability results. (For dosage units sampled in this fashion the location within the container from which they were taken should be identified. This information should be included when presenting the results.)

c. Sampling Time Considerations: The sample times should be chosen so that degradation can be adequately characterized if it occurs, i.e., at sufficient frequency to determine with reasonable assurance the nature of the degradation curve. Usually, the relationship can be adequately represented by a linear, quadratic, or cubic function on an arithmetic or a logarithmic scale (Section III.C.6).

For predictably stable drugs, stability testing may be performed at three-month intervals during the first year, six-month intervals during the second, and yearly thereafter.

The degradation curve is estimated most precisely (in terms of the width of the confidence intervals about the estimated curve, as illustrated in Figure 1) around the average of the sampling times included in the study. For this reason, sampling more frequently around the end of the desired expiration dating period is encouraged, since this will increase the average sampling time toward the desired expiration dating period.

2. Data Analysis and Interpretation: Long-Term Studies

When establishing the expiration dating period for an individual batch, consideration is given to the observed pattern of degradation for the quantitative drug characteristic of interest (e.g. strength) and to the

precision by which it is estimated. An acceptable approach, for drug characteristics that are expected to decrease with time, is to determine the time at which the 95% one-side lower confidence limit (sometimes called the 95% lower confidence bound) for the mean degradation curve intersects the acceptable lower specification limit. For the case of a linear degradation curve, the 95% one-sided lower confidence limit is the one-sided analogue of the two-sided limits described in Snedecor and Cochran [12], page 153, section 6.11. In the example shown in Figure 1, an expiration dating period of four years would be granted. For drug characteristics expected to increase with time (e.g. there may be an upper limit on the amount of certain degradation products), the 95% one-sided upper confidence limit would be used.

For drug characteristics with both an upper and a lower specification limit, there may be special cases where it would be appropriate to use the two-sided 95% confidence limits. As an example, suppose the drug characteristic of interest was concentration of unchanged active ingredient for a solution. Chemical degradation of the active ingredient would decrease the concentration. On the other hand, evaporation of the solvent (possibly resulting from the closure) would increase the concentration. Since both possiblities must be allowed for, two-sided confidence limits would be appropriate. (Of course, in the above example, if both mechanisms were acting the concentration might, e.g., decrease initially and then increase. In this case, the degradation pattern would not be linear and more complicated statistical methods would be needed.)

If this approach is used, we may be 95% confident that the average drug characteristic (e.g., strength) of the dosage units in the batch is within specifications up to the end of the expiration dating period. If it is desired to ensure that the characteristics of a large proportion (e.g., 90%) of the individual dosage units are within specifications, different statistical methods are needed. See, e.g., Easterling [13].

If batch-to-batch variability is small, i.e., the relationship between strength and time is essentially the same from batch to batch, it would be advantageous to combine the data into one overall estimate. Combining the data should be supported by a preliminary test of batch similarity. The similarity of the degradation curves for each batch tested should be assessed by applying statistical tests of the equality of slopes and of zero time intercepts. The level of significance of the test should be chosen so that the decision to combine is only made if there is strong evidence in favor of combining. Bancroft [14] has

recommended a level of significance of 0.25 for preliminary statistical tests similar to this.

If the preliminary statistical test rejects the hypothesis of batch similarity because of unequal initial strengths, it may still be possible to establish that the slopes are parallel, and in this case the data may be combined for purposes of estimating the common slope. The individual expiration dating period for each batch may then be determined by taking into account the initial potency values. For example, if the degradation curve, assumed here to be linear, estimates that a product initially at 100% strength would be reduced to 90% potency in 5 years, a product with initial potency of only 96% would be estimated to have an expiration dating period of 3 years.

If data from several batches can be combined, it is advantageous to include as many batches as feasible, because confidence limits about the estimated slope or the estimated degradation curve will become narrower as the number of batches increases, usually resulting in a longer expiration dating period.

If it is inappropriate to combine data from several batches, the overall expiration date may depend on the minimum time a batch may be expected to remain within acceptable limits.

3. Precautions To Be Observed in Extrapolation Beyond the Actual Data Period

The statistical methods for determining an expiration period beyond the range of storage times actually observed are the same as for determining an expiration period within the observed range. However, the a priori correctness of the assumed pattern of degradation as a function of time is crucial in the case of extrapolation beyond the observed range.

When estimating an assumed degradation line or curve over the observed range of data, the data themselves provide a check on the correctness of the assumed relationship, and statistical methods may be available to test the goodness of fit of the data to the assumed degradation line or curve. No such internal check is available beyond the range of observed data.

As an example, suppose it has been assumed that the relationship between log strength and time is a straight line, but in fact the true relationship is a curve. It may be that over the range of the observed data, the true curve is close enough to a straight line so that no serious error is made by approximating the degradation relationship as a

straight line. However, between the last observed data points and the estimated expiration time, the true curve may diverge from a straight line enough to have an important effect on the estimated expiration time.

For extrapolation beyond the observed range to be valid, the assumed degradation relationship must continue to apply through the estimated expiration dating period. For this reason, an expiration dating period granted on the basis of extrapolation should always be verified by actual stability data up to the granted expiration time as soon as these data become available.

E. Alternate Protocol

If for any stated reason the approach proposed in these guidelines is not suitable for the new drug or biological product under development, a different stability study protocol should be designed by the sponsor during clinical phases of investigation (Section II.D). The sponsor should assure that the protocol is acceptable to the reviewers in the Center for Drugs and Biologics.

IV. INVESTIGATIONAL NEW DRUGS (IND's)

Studies conducted during development of a drug or biological product do not necessarily follow a rigid separation into Phases 1, 2, and 3, but the following is presented as a general IND development sequence that is intended to provide guidance for the development of product stability information during the investigational phases.

A. IND Phase 1

The stability characteristics of the bulk drug substance should be determined at the earliest possible time to support conditions of use of the bulk drug in toxicity studies (i.e. pre-IND studies, mixed with feed, etc.) and the stability of the drug substance in the initial formulations proposed for use in clinical pharmacological studies. This information should be included in the initial IND submission to FDA. Required stability information would be limited to that needed to demonstrate that the product would be stable for the duration of the investigation. If necessary, additional data may be submitted as they become available during the course of the clinical study.

B. IND Phase 2

Stability studies on the investigational formulations should be well underway by the end of Phase 2.

Drug or biological formulations developed during Phase 2 (as well as Phase 3) should be based upon the stability information developed from studies on bulk drug substance and/or on the stability of formulations prepared in experimental studies. The objectives of stability testing during Phases 1 and 2 are (a) to evalute the stability of the investigational formulations used in the clinical trials and (b) to obtain the additional information needed to develop a final formulation (e.g., compatibility studies of potential interactive effects between the drug substance(s) and other components of the system). This information should be summarized and submitted to the IND when available.

C. IND Phase 3

The emphasis in stability testing during Phase 3 is on final formulations in their probable market packaging, on expiration dating, and on the study of degradation products when encountered. Studies to support the proposed expiration dating period should be completed, where possible, during Phase 3 for inclusion in the initial NDA, Form 5 or 6, or PLA for biological products.

V. NEW DRUG APPLICATIONS (NDA's)

A. Original Submissions

Ordinarily an original NDA submission should contain primary stability data and other suitable data (e.g., accelerated data) that, when subjected to appropriate statistical analysis (figure 1), support the proposed expiration date and the proposed storage conditions for labeling. This must be accompanied by the standard commitment to continue the stability study (See "Definitions"). As a condition for approval it is expected that samples of the first three production lots will be placed in the stability program for the full length of the expiration dating period for confirmation of the dating period assigned.

A full report on stability of the bulk drug substance should provide information outlined in Sections III.B and III.C.6 of the guidelines on general stability characteristics and degradation products.

Stability studies conducted for all formulations utilized during clinical investigations should be summarized as described in Sections III.A, III.C, III.D, and VII, of these guidelines.

The lots used for stability testing should comply fully with proposed specifications for the product in its market package. Studies to support an expiration dating period under defined storage conditions using several lots representative of the

product to be marketed should have been started as early as possible prior to the NDA.

It should be appreciated that a reviewer cannot refer to information or make any comparisons with data contained in another application. Stability data submitted in a Paper NDA must be complete within themselves.

B. Computation of Expiration Date

The computation of the expiration date of the new drug production lot should begin at the time of quality control release of that lot, and the date of such release should generally not exceed 30 days from the production date regardless of the packaging date.

If the production lot contains reprocessed material, the expiration date shall be computed from the production date of the oldest reprocessed lot contained in the new lot.

C. Abbreviated New Drug Applications (ANDA's)

In the case of drug products that have been approved for marketing under an ANDA, information such as stress testing, references to publications, and comparative stability data for the proposed drug product with that of the innovator's drug product (especially when utilized in bioavailability/bioequivalence studies) are acceptable.

In the absence of sufficient room temperature data, stress testing will be accepted for granting a tentative expiration dating period, provided adequate information concerning stability of the drug substance has been submitted. The recommended stress testing conditions are:

- 37-40°C (or as appropriate for a particular drug product, e.g., suppositories), and
- 75 percent relative humidity (where appropriate).

Samples should be analyzed initially and at 1, 2, and 3 months. The parameters described under Section III.C should be considered when collecting stability data for various drug products. Available long-term stability data should be included and reported as outlined in section VII of the guideline.

If the results are satisfactory, a tentative expiration dating period of 12 to 18 months will be granted for drug products packaged in unit-dose containers. For drug products packaged in other container-closure systems, the tentative expiration dating period will be 24 months.

The submission should include a signed statement that:

1. Stability studies as outlined below will be performed.

   The first three production lots of the product should be placed on stability testing. Controlled room temperature stability testing should be done initially, at 3, 6, 9, 12, 18, and 24 months, and yearly thereafter until the desired expiration date of the product is reached. If more than one package size is marketed, the first three production lots of the smallest and the largest size (e.g., 3 lots of 100-tablet bottles and 3 lots of 500-tablet bottles) should be tested. Also, if more than one container/closure system is used for a particular size, stability data in each container/closure system should be submitted. Yearly thereafter, one production batch should be added to the stability program.

2. Results will be submitted as they become available.

3. Any lots that fall out of specifications will be withdrawn promptly from the market, and must be reported to FDA under 21 CFR 310.300(b)(1).

D. SUPPLEMENTS TO NEW DRUG APPLICATIONS

A Supplement may be classified under several categories as indicated below:

1. Changes in Formulation, Supplier, and Container-Closure

   A supplement that proposes a change in the drug's formulation, in the supplier of a drug substance, or in the container-closure system for a marketed drug product, will usually require the development of data to show that this change does not adversely affect stability. Usually, accelerated data demonstrating comparability with the previously approved drug product, plus the standard commitment to continue the stability study will suffice. For significant changes of products known to be relatively unstable, six months' data at the normal recommended storage temperature, as well as the data from accelerated conditions, may also be required.

   If the data give no reason to believe the proposed change will alter the stability of the product, the previously approved expiration dating period may be used.

2. Interchangeability of HDPE Containers

   A special case is the interchangeability of High Density Polyethylene (HDPE) containers for capsules and tablets that

meet standards and tests described in the U.S.P. In this instance, a supplement may be approved with no advance stability data, provided there is a commitment to do the stability testing.

3. New Manufacturing Facilities

For a change limited to a new manufacturing facility for the identical drug product using similar equipment, a commitment should be submitted to conduct stability studies on at least the first three production lots based on the approved protocol. Ordinarily, the already approved expiration dating period may be used under these circumstances.

4. Reprocessed Material

A supplement providing for the use of reprocessed material should include data to demonstrate that the reprocessed product has identity, strength, quality, and purity comparable to that approved in the NDA for the designated expiration dating period. Also, the standard commitment to continue the stability study should be submitted.

5. New Container Fabricator

When a new plastic container fabricator is proposed, with no change in materials or specifications, the applicant should have full specifications for the approved container to supply to the new fabricator. The new fabricator should submit manufacturing information to the applicant (or directly to the FDA), and should agree to inform the drug manufacturer immediately of any change in resin formulation. The applicant should provide the standard commitment to initiate stability studies on several production lots packaged in the container from the new fabricator. Under these circumstances, accelerated or preliminary stability data are not required, and the already approved expiration dating period may be used.

VI. PRODUCT LICENSE APPLICATION FOR BIOLOGICAL PRODUCTS (PLA)

A. General Guidelines for Biological Product Stability Studies

The active components of biological products are usually protein derived or other organic substances. Such substances are usually heat sensitive and require refrigeration or freezing to protect the potency of the product. Therefore, the methodologies and statistical analyses used for determining the stability characteristics and expiration dating period for drug products are not necessarily applicable to biological products.

Because of the complexity and variety of the composition of biological products, requirements for determining their stability may differ markedly among different types of products.

Documentation of biological product stability is required for all new biological products and when significant changes are made to the composition or to the container and closure systems for currently approved biologicals. The descriptions which follow offer guidance regarding when stability data is required for biologicals. All proposals and submissions related to biological product stability should either accompany the product license application in an original submission for licensure or be submitted as an amendment to an existing product license application. Each submission will be considered on an individual basis depending on the composition and characteristics of the product.

B. Original Submission

1. Studies Submitted with Application

Studies to support the expiration dating period of a biological product using at least 3 lots representative of the product to be marketed under defined storage conditions should be submitted at the time of license application filing. These lots should comply fully with proposed specifications for the product in its market package. Stability data from at least three lots is usually required for licensure approval.

2. Supportive Data

The approved expiration dating period of a biological product is normally based upon the interval of time for which data are available under the storage conditions stated in the labeling. Studies that address the stability of the product when in bulk storage (prior to filling) may be considered to support the expiration dating period of the finished dosage form. In addition, the effects of temperature fluctuations that may be encountered during shipment of the product should be determined.

3. Expiration Dating Period Granted with Commitment

In some instances, the stability data may not cover the full time period desired. It is possible to grant the desired expiration dating period provided that all data and information clearly support this conclusion and there is a sufficient lead time for development of data covering the desired expiration dating period. The standard commitment to continue the stability study must also be submitted.

C. Amendments

1. Change in Formulation and Container-Closure

An amendment to an approved PLA that proposes a change in the product's formulation, including, for example, the culture media for growing live organisms, or the container-closure system for the marketed product, will usually require the development of data to show that the proposed change has not adversely affected the stability of the product. In certain instances, accelerated storage data demonstrating comparability with the previously approved product plus the standard commitment will suffice. For certain biological products known to be relatively unstable this may require a minimum of six months' data at the normal recommended storage temperature together with data from accelerated conditions.

2. New Manufacturing Facility

For a change limited to a new manufacturing facility for the same licensed product using similar equipment, a commitment should be submitted to conduct stability studies on a minimum of the first three lots produced in the new facility. Ordinarily, the previously approved expiration dating period may be used under these circumstances.

3. Extension of Expiration Dating Period

An amendment requesting an extension in the expiration dating period should be accompanied by supporting updated stability data.

4. Reprocessed Material

When appropriate, an amendment providing for the use of reprocessed material should include data to assure that the reprocessed product will meet final product specifications. The standard commitment to subject any lots of the product made from reprocessed material to stability testing should accompany the amendment.

VII. CONTENT OF STABILITY REPORTS

It is suggested that stability reports include the following information and data to facilitate decisions concerning the stability proposals:

A. General Product Information

1. Name of drug and drug product or biological product.

2. Dosage form and strength.

3. Labeling and formulation. (The application should provide a table of specific formulations under study when more than one formulation has been studied.)

4. Composition, type, and size of container-closure.

B. Specifications and Test Methodology Information

1. Physical, chemical, and microbiological characteristics and prior submission specifications (or specific references to NDA or USP).

2. Test methodology used (or specific reference to NDA, prior submissions, or USP) for each sample tested.

3. Information on accuracy, precision, and suitability of the methodology (cited by reference to appropriate sections).

4. For biological products, a description of the potency test(s) for measuring biological activity, including specifications for potency determination.

C. Study Design and Study Conditions

1. Description of the sampling plan, including:

   a. Batches and number selected,
   b. Containers and number selected,
   c. Number of dosage units selected and whether tests were conducted on individual units or composites of individual units,
   d. Sampling times, and
   e. Testing of drug or biological products for reconstitution at the time of dispensing (as directed on the labeling) as well as after they are reconstituted.

2. Expected duration of the study.

3. Conditions of storage of the product under study (temperature, humidity, light).

D. Stability Data/Information

1. Lot number (research, pilot, production) and associated manufacturing date.

2. For antibiotic dosage forms, the age of the bulk active drug substance(s) used in manufacturing the lot.

3. Analytical data and source of each data point, e.g., lot, container, composite, etc. Pooled estimates may be submitted if individual data points are provided.

4. Relevant information on previous formulations or container-closure systems should be included (or referenced, if previously submitted).

E. Data Analysis and Conclusions

1. Documentation of appropriate statistical methods and formulas used in the analysis.

2. Evaluation of data, including calculations, statistical analysis, plots, or graphics.

3. Results of statistical tests used in arriving at microbiological potency estimates.

4. Proposed expiration dating period and its justification.

5. Release specifications (establishment of acceptable minimum potency at the time of initial release for full expiration dating period to be warranted).

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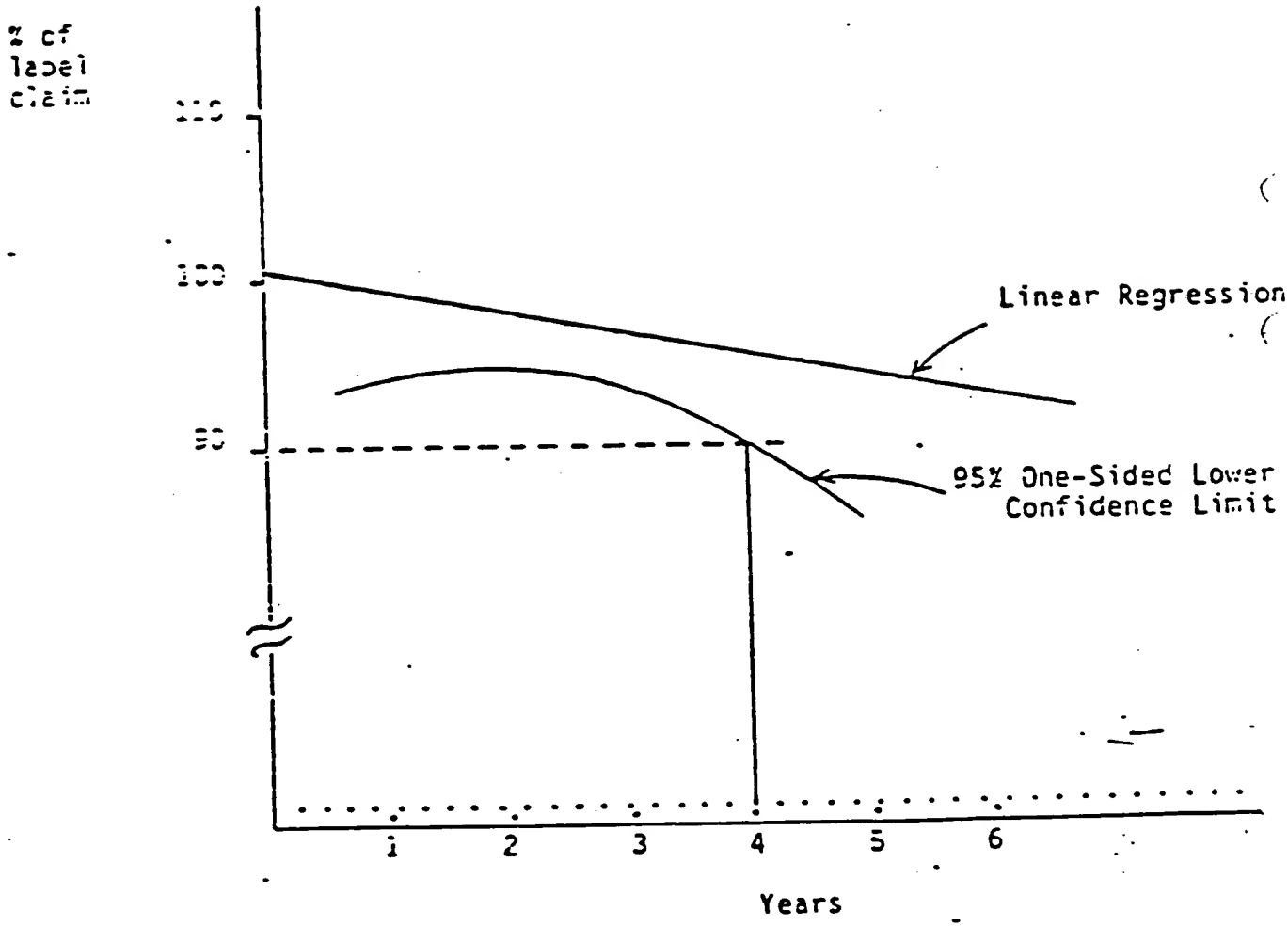
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Figure 1